REMARKS/ARGUMENTS

In the specification, paragraphs [0007], [0027] and [0072] have been amended to correct minor typographical errors.

Claims 1-7, 9, 11-23, 26 and 28-32 are pending and stand rejected in this application. Claims 8, 10, 24, 25 and 27 were previously deleted. Claims 1, 11, 12, 13, 15, 17, 22, 28 and 32 have been amended herein, and the objections to the Information Disclosure Statement and rejections of the claims have been addressed. Elements of claim 6 were incorporated into claim 1; therefore, claim 6 has been cancelled. The proposed amendments to the application and the comments in the office action regarding claims 1-7, 9, 11-23, 26 and 28-32 are now addressed in turn.

Claim Rejections Under 35 USC § 112, 2nd Paragraph

Claims 1-7, 9, 11-23, 26, and 28-32 were rejected under 35 USC § 112 2nd Paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 22, 32, and all claims dependent therefrom were rejected as being allegedly indefinite due to the lack of clarity of the claim language failing to recite a final process step that agrees back with the preamble. Applicants have amended claims 1 and 22 to further clarify the instant invention by substituting the phrase "primer pairs in said subset have been thereby designed" for the phrase "subset of primer pairs may be used". Applicants have also amended claim 32 to include the phrase "wherein said primer pairs in said subset have been thereby designed for amplifying said target nucleic acid sequence." No new matter has been added by virtue of these amendments. Applicants believe that the amendments have rendered the rejection moot and respectfully request its withdrawal.

Claims 1, 22, 32, and all claims dependent therefrom were rejected as being allegedly confusing due to lack of claim language for addressing the intended utility of "said removed sequences". In addition, the Examiner alleges that it is unclear what Applicants intend the removing

repeat regions step to accomplish in the claimed invention. Applicants traverse the instant rejection. The claimed invention is directed to selecting primer pairs by removing regions of a reference sequence whereby the unremoved regions of the reference sequence are used to design primer pairs. Applicants respectfully point out that the "removed sequences" are not used in the primer selection process, and that is the basis for their exclusion from the subsequent steps of the instantly claimed invention. Applicants further submit that the purpose of the removing repeat regions step is, as would be apparent to one of ordinary skill in the art, to remove repeat regions from the reference sequence in order to facilitate the primer design process. If there are no repeat regions in the reference sequence, then none would be removed and, in that particular instance, the reference sequence would be identical to the yielded unremoved sequence. Applicants respectfully assert that this fact does not in any way conflict with or make indefinite the language of the instant claims, as nowhere in the claims is it stated that the "reference sequence" must be different from the "unremoved reference sequence". Applicants therefore respectfully request the withdrawal of the instant rejection.

Claim 1 and all claims dependent therefrom were rejected as being allegedly vague and indefinite due to use of the phrase "having reduced overlap". Applicants have amended claim 1 to more particularly point out the criteria/range that encompasses the phrase "having reduced overlap" by addition of the phrase "such that amplicons corresponding to said subset of primer pairs overlap by less than about 5%". This phrase has also been added to further clarify claims 22 and 32. No new matter is added by virtue of these amendments (see paragraphs [0033], [0040], [0072] and original claim 6). Applicants believe that the instant rejection has been overcome in view of the amendments to claims 1, 22 and 32, and respectfully request its withdrawal.

Claim 1 and all claims dependent therefrom were further rejected as being allegedly vague and indefinite based on the inclusion of optional type language in the previous amendment to claim 1. Applicants have amended claim 1 to further clarify the claimed invention by removal of the optional type language and submit that the instant rejection has been rendered moot in view of the amendment.

Claims 1, 18 and 19 were rejected as being allegedly vague and indefinite based on the recitation of the phrases "target sequence" and "reference sequence". The office action further alleged that the claim language fails to maintain consistent terminology. The Applicants respectfully disagree. The method of claim 1 is directed to designing primer pairs for amplification of a target sequence by selecting a reference sequence and, through a series of recited steps, using the reference sequence to design primer pairs for amplification of the target sequence. Thus, as would be clear to one of ordinary skill in the art, the reference sequence rather than the target sequence is used to design primer pairs for amplification of the target sequence. It is therefore unclear to the Applicants why the Examiner requests further claim language. However, in the interest of furthering the prosecution of the instant application, Applicants have amended claim 1 to further clarify the relationship between the "target sequence" and the "reference sequence" of the instant invention. Specifically, the phrase "using a reference sequence" was added to the preamble. No new matter was added by virtue of the amendment, which is fully supported by the instant specification (see *e.g.* paragraphs [0020], [0047] and [0057]). Further, contrary to what is alleged in the office action, Applicants submit that the claim language does maintain consistent language terminology, with the primer pairs being designed for amplification of the target sequence through a process using the reference sequence. Applicants believe that the rejection has been overcome by the amendment and arguments presented herein, and respectfully request its withdrawal.

Claims 11, 28, and all claims dependent therefrom were rejected as being allegedly vague and indefinite with regards to the phrase "a minimal or substantially minimal number of primer pairs". Applicants arguments in the previous amendment to the present applications were found unpersuasive by the Examiner due to the alleged absence of the criteria required for the determination of the actual number of primer pairs. Applicants have amended claim 11 by substituting the phrase "minimal or substantially minimal number of primer pairs required to amplify said target sequence" with the phrase "lower cost than any other subset of primer pairs from said set of primers". In addition, Applicants have amended claim 28 by substituting the phrase "with a minimal or substantially minimal number of primer pairs required to amplify said target

sequence" with the phrase "according to at least one parameter selected from the group of overlap length, gaps between pairs of primer pairs, and necessity of adding another primer pair to the subset." These amendments are fully supported by the instant specification (see paragraphs [0042], [0072], [0074], Figure 3, and original claim 13). Applicants submit that the rejection has been rendered moot by the amendments and respectfully request its withdrawal.

Claim 32 was rejected as being allegedly indefinite due to the lack of clarity of the claim language failing to recite a final process step that agrees back with the preamble. Applicants have amended claim 32 as described above to further clarify the instant invention by substituting the phrase "primer pairs in said subset have been thereby designed" for the phrase "subset of primer pairs may be used". No new matter has been added by virtue of this amendment. Applicants believe that the amendment renders the rejection moot and respectfully request its withdrawal.

Claims 15-17 were rejected for allegedly having insufficient antecedent basis for the limitation "said computer program". Applicants have amended claims 15 and 17 to correct the lack of antecedent basis by substituting the phrase "said computer program" with the phrase "a computer program". Applicants submit that the rejections have been rendered moot by virtue of the amendments to claims 15 and 17, and respectfully request their withdrawal.

Claim Rejections Under 35 USC § 103

Claims 1-7, 9, 11-14, 18-23, 26, 28, 29, and 32 were rejected under 35 USC § 103(a) as being allegedly unpatentable over Harris (Genome Research (1997) 7:754-762) in view of Primer3 (release 0.6 (1997)). The rejection on this basis is respectfully traversed. In order for a reference or a combination of references to support a *prima facie* case of obviousness, the reference(s) must (a) disclose all elements of the claimed invention, (b) suggest or motivate one of skill in the art to combine or modify those elements to yield the claimed combination, and (c) provide a reasonable expectation of success should the claimed combination be carried out. The cited references, alone or in combination, fail to teach the claimed invention as currently amended.

The invention as claimed with the amendment herein is directed to selecting a primer subset based on criteria including "reduced overlap". The Examiner has based his rejection on a misreading of the term "reduced overlap" as described in the instant application and its meaning as described in the Primer3 reference. The present invention teaches a method of selecting a subset of primer pairs whose corresponding amplicons overlap by less than about 5%. The office action correctly points out that Harris does not describe the details for primer selection, and therefore fails to teach this limitation of the present invention. Although Primer3 allegedly describes certain criteria for primer selection, nowhere is there any description of a primer selection criteria that involves using the overlap of amplicons corresponding to the primer pairs. The Examiner refers to page 5, lines 1-9 as an example of a criteria involving "reduced overlap", however this section refers to overlap of the primer sequences and "excluded regions", not overlap of amplicons. In fact, nowhere in the Primer3 or Harris references is there any description or teaching regarding overlap of amplicons. Therefore, neither Harris nor Primer3, either alone or in combination, teaches every element of the claimed invention. As such, even if one of skill were motivated to combine the teachings of Harris with those of Primer3, they would not arrive at the present invention. Accordingly, Applicants respectfully request withdrawal of the rejection on this basis.

Further, with respect to claims 2, 3 and 21, the present invention teaches that a primer length is selected to be between about 28 nucleotides and about 36 nucleotides, and that a primer melting temperature is selected to be between about 72°C and about 88°C. Neither reference alone or in combination teaches or suggests selecting primer pairs based on these ranges of primer lengths and primer melting temperatures. In contrast, Primer3 discloses an "optimum" primer size of 20 nucleotides, a default minimum primer size of 18 nucleotides, a default maximum primer size of 27 nucleotides, and further imposes a limit such that this parameter cannot be larger than 35 nucleotides (page 7, lines 8-20). As such, Applicants submit that not only is the claimed invention not disclosed in the cited references, but that the disclosure of Primer3 in fact *teaches away* from the instant invention with regards to primer length. Further, Primer3 discloses an "optimum" primer melting temperature of 60°C, a default minimum primer melting temperature of 57°C, and a default maximum melting temperature of 63°C (page 7, lines 21-35), and so does not teach a primer melting temperature range of about 72°C to about 88°C. As noted above, the Harris reference does not describe the details for primer selection, so does not teach any ranges for primer length or melting temperature. Since each and every element of the claimed invention is not taught by the cited

references, either alone or in combination, Applicants respectfully request withdrawal of the instant rejection with respect to claims 2, 3 and 21.

With respect to claim 23, the present invention teaches that the step of removing repeat regions from the reference sequence is performed by a computer program that references a database. The office action states that "Genotator is linked to several reference databases", citing pages 756-757 and Figures 5 and 8 of the reference. Applicants respectfully disagree. There is no indication in the Harris reference that Genotator is linked to any database at all. At best, the text regarding Figure 5 states that a human tissue factor gene sequence that was analyzed using Genotator was obtained from GenBank, but the text does not state that Genotator is actually linked to GenBank, or any other database. Likewise, the Primer 3 reference does not disclose a functionality that links the Primer3 software to a database. Therefore, even if one of skill were to combine the teachings of Harris with those of Primer3, they would not arrive at the present invention of claim 23. As such, Applicants respectfully request withdrawal of the instant rejection with respect to claim 23.

Information Disclosure Statement

Several cited references on the information disclosure statement were lined through because the dates that the information was publicly available could allegedly not be confirmed. Applicants previously submitted that the hard copy print-outs with the dates of printing shown in the lower right-hand corner indicate the dates that such information was publicly available, but the argument was found to be unpersuasive by the Examiner. The only reason provided for the rejection of Applicants argument was that the cited reference "Long PCR reagents & guidelines" could not be found at the indicated website. Applicants respectfully traverse the objection with reference to MPEP §707.05e, which defines an electronic document as "one that can be retrieved from an online source ... or sources found on electronic storage media". The MPEP further states that copies of electronic documents must be retained if the same document may not be available for retrieval in the future, and that this is of particular importance for sources such as the Internet and online databases. As such, it is clear that the USPTO recognizes that some references that were originally obtained from an online source may not be continually available from that source. The MPEP does

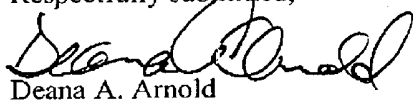
not, however, say that the online unavailability of a reference that was originally obtained online renders the reference immaterial or unsuitable for inclusion in an IDS. In addition, MPEP §2128 states that "Prior art disclosures on the Internet or on an online database are considered to be publicly available as of the date the item was publicly posted. If the publication *does not* include a publication date (or *retrieval date*), it cannot be relied upon as prior art under 35 U.S.C. 102(a) or (b), although it may be relied upon to provide evidence regarding the state of the art." [emphases added] The references submitted by the Applicants do include a retrieval date as indicated previously, and therefore clearly indicate a date at which the reference was publicly available. As such, Applicants respectfully request reconsideration of the references in question.

Applicants also respectfully point out that there is a typographical error in the Notice of References Cited included with the office action dated April 19, 2004. Specifically, "Genotator: A Workbench for Sequence Annotation" was published in Genome Research, not Genome Methods. Applicants respectfully request a correction be made in the record with regards to this reference.

Conclusion

For the reasons set forth above, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-625-4603.

Respectfully submitted,



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